**SEARLE**

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SEARLE
5200 OLD ORCHARD ROAD
SKOKIE, ILLINOIS 60077

June 5, 2000

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20852

**Re: ICH Q1A(R) STEP 2 document**
**(Docket No. 93D-0139)**

Please find enclosed two copies of comments provided by Pharmacia Corporation concerning the referenced document. In general, the draft document was found to be well written and the added clarity and consistency it will provide is appreciated.

We wish to thank the agency for the opportunity to provide input and hope our comments are helpful.

Respectfully submitted,

Dr. Kevin Siver, Ph.D.
Global Stability Manager (Searle)
Pharma Global Quality & Compliance

Attachment

93D-0139

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## COMMENTS ON ICH Q1A(R) STEP 2 DOCUMENT
## (Docket No. 93D-0139)

### DRUG SUBSTANCE

*Stress testing (page 21448)*

- In the first paragraph, third sentence, **delete** the sentence "The severe conditions that may by encountered during distribution can be covered by stress testing."

  Shipping condition excursions should not be **equated** with the severe conditions that are used in stress testing. This is not the purpose for stress testing. As stated in "Storage Conditions" sections for both drug substance and drug product, the accelerated or intermediate storage conditions may be used to evaluate shipping condition excursions.

*Selection of Batches (page 21448)*

- In the second paragraph, **delete** the "...used in clinical studies and of the quality of material..." clause.

  The formal stability studies should address quality issues related to the long term stability of drug substance. The batches used should represent future production capabilities. Differences in profiles between bio- and production batches should be addressed elsewhere.

*Storage conditions (page 21449)*

- In the Freezer Condition table, **replace** "–20 °C ± 5 °C" with "–15 °C ± 5 °C".

  This would align with the upper limit of the USP specified range for a freezer of –25 °C to –10 °C and with the next section for storage below –20 °C.

*Stability Commitment (page 21449)*

- The clarification of terminology and expectations provided in this section is much appreciated. However, the use of the terminology "stability protocol" in the last paragraph, could be misunderstood to include accelerated and/or intermediate studies. Emphasis should be provided that only the long-term study condition (e.g. 25 °C/60% RH) is implied.

### DRUG PRODUCT

*Storage conditions (page 21451)*

- There is no guidance provided for the situation when accelerated and intermediate studies **both fail** significant change criteria while, at the same time, the long-term study supports a 24-month or longer shelf-life.

*Drug Products Packaged in Semipermeable Containers (page 21451)*

- Clarity should be provided as to why the intermediate storage condition is listed as "30 °C ± 2 °/60% RH ± 5% RH"? Shouldn't the relative humidity for the intermediate condition be somewhere between long-term and accelerated humidity specifications of 40% RH and 25% RH, respectively?

- In the first paragraph after table, reference is made to calculations using permeation coefficients. An example of these calculations should be provided similar to the example provided for determining percentage water loss.

*Storage conditions (page 21452)*

- In the *Freezer Condition* table, **replace** "−20 °C ± 5 °C" with "−15 °C ± 5 °C".

  This would align with the upper limit of the USP specified range for a freezer of −25 °C to −10 °C and with the next section for storage below −20 °C.

*Stability Commitment (page 21452)*

- Alternatives 2 and 3: should be reworded to state clearly that only the long-term condition should be carried through the proposed shelf life. The use of the term "long-term and accelerated stability studies" relating to "through proposed shelf life" is confusing. Accelerated and intermediate conditions are only carried out for 6 and 12 months, respectively.

**Annex 1**

*Glossary And Information*

*Drug substance (page 21453)*

- Should **replace** "unformulated drug substance" with "unformulated active pharmaceutical ingredient".

*Retest Period (page 21453)*

- In the last sentence, **replace** "and then used immediately" with "before use".

*Storage Condition Tolerances (page 21453)*

*Retest Period (page 21453)*

- In the last sentence, **replace** "and then used immediately" with "before use".

*Storage Condition Tolerances (page 21453)*

- Clarification should be provided that monitoring of conditions is only necessary when control of conditions is required.

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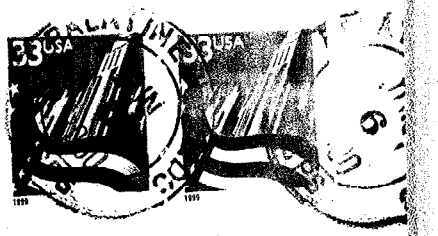


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